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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|----------------------|---------------------|------------------|
| 09/602,775 | 06/23/2000 | Neil R. Cashman | 50111/002002 | 9735 |

21559 7590 09/21/2004

CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER

WINKLER, ULRIKE

| ART UNIT | PAPER NUMBER |
|----------|--------------|
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1648

DATE MAILED: 09/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | | |
|------------------------|--------------------------------------|---------------------------------------|--|
| Advisory Action | Application No. 09/602,775 | Applicant(s) CASHMAN ET AL. | |
| | Examiner Ulrike Winkler | Art Unit 1648 | |

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 22 July 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

- a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
- b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
- ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on 22 July 2004. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.
2. ☐ The proposed amendment(s) will not be entered because:
- (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);
 - (b) ☐ they raise the issue of new matter (see Note below);
 - (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
 - (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.
4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
5. ☐ The a) ☐ affidavit, b) ☐ exhibit, or c) ☐ request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.
6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.
7. ☒ For purposes of Appeal, the proposed amendment(s) a) ☐ will not be entered or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____.

Claim(s) objected to: _____.

Claim(s) rejected: 1-17, 80-82.

Claim(s) withdrawn from consideration: 18-79.

8. ☐ The drawing correction filed on _____ is a) ☐ approved or b) ☐ disapproved by the Examiner.
9. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____.
10. ☐ Other: _____

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The rejection of claims 1-8, 10-17, 80-82 under 35 U.S.C. 102(b) as being anticipated by Korth et al. (Nature, 1997, IDS Paper No. 7) is **maintained** for reasons of record.

Applicants arguments are that the 15B3 antibody and the 6H4 antibody do not bind to peptides that comprising a YYX epitope. Applicants provide appendix A which shows peptide segments of 13 amino acids with sequential shift of 2 amino acids. Applicants use their appendix A in conjunction with Figure 2a (Korth et al. Nature 1997) to indicate that neither the 6H4 or 12B3 antibody bind to all YYX epitopes in the prion peptide, and because they do not bind to all YYX epitopes in the prion protein they do not fall within the bounds of the instantly claimed invention. Applicants use the same reason to indicate that the 15B3 antibody binds to peptides that do not comprise the YYX epitope. A review of the Korth et al. reference indicates that the 15B3 antibody recognizes a three dimensional epitope in the prion protein and this antibody recognizes a peptide comprising the YYX epitope. The 2nd epitope region bound by the 15B3 antibody covers the peptide numbers #73, #74 and #75 representing the following sequences PNQVYYRPVDQYS, QVYYRPVDQYSNQ and YYRPVDQYSNQNN. The 6H4 antibody binds to the single linear epitope DYEDRYYRE. Therefore, Applicants arguments that the reference fails to disclose an antibody that binds a peptide comprising a YYX epitope is not convincing.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., binding all YYX epitopes in the prion protein or all YYX epitopes in all peptides) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations

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from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicants also point to the Paramothiotis et al. reference (applicants own work) as providing evidence that the 6H4 antibody binds to different epitopes than the instantly claimed antibodies. A review figure 3a in Paramothiotis et al. indicates that none of the antibodies including Applicants antibodies meet the limitation that the antibody bind all YYX comprising epitopes. Figure 3a, the experimental design is to incubate the samples with the designated antibody first and then to use antibodies attached to magnetic beads as a way of immunoprecipitation. If the soluble antibody binds the epitope when then the epitope is not available for immunoprecipitation. Here the use of the 6H4 antibody prevented immunoprecipitation with the 6H4 antibody but not the 1A12 or 17D10 antibody, indicating as Applicant pointed out that the antibodies recognize different epitopes. The 1A12 antibody does not block immunoprecipitation with any of the antibodies tested indicating that this antibody recognizes a different epitope and one not necessarily comprising the YYX epitope in the prion protein. The 17D10 antibody blocks perception with the 1A12 and 17D10 indicating that the antibody recognizes different epitopes, yet none of Applicants own antibodies is capable of recognizing all YYX comprising epitopes in the prion protein.

Korth et al. disclose monoclonal antibodies 15B3 recognize a YYX epitope (see figure 2), the reference discloses hybridoma cell lines for the production of the antibodies. The 15B3 antibody binds selectively to the PrP^{Sc} from various species without the need to digest the sample with proteinase K (see page 77, last paragraph). The 15B3 antibody recognizes a three dimensional epitope that comprises the YYX epitope. The reference discloses

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immunoprecipitation experiments (see figure 1 and 2; page 77 characterization of antibodies) indicating that the antibody binding range of the antibody is between 10^{-6} M between 10^{-8} M. Therefore, the rejections are maintained as being anticipated by Korth et al.

The rejection of claims 1-17, 80-82 under 35 U.S.C. 102(a) as being anticipated by Korth et al. (WO 98/37210, see IDS) or under 35 U.S.C. 102(b) by Korth et al. (EP 0 861 900, see IDS) **is maintained** for reasons of record. See response above.

The rejection of claims 2 and 11 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention **is maintained** for reasons of record.

Applicant's argument is that the "phrase antibody does not specifically bind PrPC" is straightforward and the specification identifies exemplary antibodies and one of skill in the art would recognize what is meant by the term. Given the phrase in conjunction with the definition "high affinity" and "low affinity" binding (i.e. does not specifically bind) in the specification it is not so clear. "high binding affinity" defined on page 8, lines 13-15, as ranging from less than 10 μ M [10^{-5} M] to less than 10 nM [10^{-8} M]. The art generally recognizes that a binding affinity of 10 μ M [10^{-5} M] would be considered a weak interaction [see table 3.1 in Harlow et al., Antibodies: a laboratory manual, Cold Spring Harbor Laboratory (1988) page 27-28]. Based on the definition provided in the specification the "high affinity" binding encompasses binding affinities that the ordinary artisan would recognize as being a weak antibody binding interaction falling within the term "does not specifically bind". Therefore the claims remain indefinite

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because it is not clear what is encompassed by the term "does not specifically bind" especially when read in view of the definition of what constitutes a "high binding affinity" antibody. The rejection is maintained.

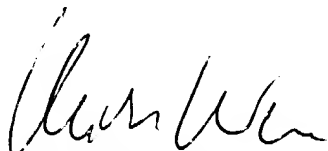
Papers related this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989). The Group 1600 Official Fax number is: (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Tech Center representative whose telephone number is (571)-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 571-272-0912. The examiner can normally be reached M-F, 8:30 am - 5 pm. The examiner can also be reached via email [ulrike.winkler@uspto.gov].

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 571-272-0902.


ULRIKE WINKLER, PH.D.
PRIMARY EXAMINER 9/17/04